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Functional and clinical evaluation of renal injury in patients treated with adjuvant chemoradiotherapy for gastric cancer: Low dose and comorbidity considerations

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ABSTRACT

Aim: To analyze the dosimetric factors affecting long-term renal function in patients with gastric cancer following postoperative radiotherapy with concomitant chemotherapy to the upper abdomen.

Methods: Between January 2005 and July 2010, 13 patients treated with three-dimensional conformal radiotherapy and concurrent fluorouracil-based chemotherapy (CRT) were included in this analysis. After a median follow-up of 55 months, creatinine, glomerular filtration rate (GFR), total kidney and left kidney volumes, before and after CRT and mercaptoacetyltriglycine (MAG3) scintigraphy, were used to evaluate the renal function and were correlated with the dosimetrics data.

Results: Significant correlations were found in the loss of left kidney volume and V35 (20.6%) ($p = 0.035$) and V40 (15.7%) ($p = 0.031$) and in the loss of relative functional contribution of the main kidney and V35 Gy ($p = 0.027$) and V40 Gy ($p = 0.019$). In patients with a slightly low basal GFR (n = 6), the relative functional contribution of the left kidney significantly decreased, regardless of the dosage.

Conclusion: Functional renal impairment without any clinical signs or symptoms can be observed in low doses after radiotherapy. Careful treatment planning and a detailed evaluation of the functional renal capacity before treatment may help to reduce late renal toxicity.

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1. Introduction

The kidney is one of the main dose-limiting organs during abdominal irradiation in cancer patients. Radiation-induced clinical renal injury to this late-responding tissue has been previously described (Cassady, 1995; Flentje, Hensley, Gademann, Menke, & Wannenmacher, 1993; Helal, Fick-Brosnahan, Reed-Gitomer, & Schrier, 2012; Kost et al., 2002; Verheij, Dewit, Valdes Olmos, & Arisz, 1994). The kidney has a physiological compensatory capacity, and many clinical signs and symptoms cannot be observed until the glomerular filtration rate (GFR) significantly decreases (Cassady, 1995). The tolerance limits for defining the probability of serious insufficiency were also described (Emami, Lyman, Brown, & Cola, 1991). However, the patient-related (i.e., diabetes, hypertension, liver or heart failure and previous kidney insufficiency), treatment-related (i.e., chemotherapy, low doses of radiotherapy) and organ-specific (spatial variation in radiosensitivity, compensatory capacity for both kidneys) effects remain unclear and need to described (Dawson et al., 2010).

We aimed to analyze the functional changes in the kidney over time and to examine their correlations with dose-volume results in gastric cancer patients receiving adjuvant chemoradiotherapy.

2. Materials and methods

This retrospective study was approved by the Ethical Committee of Marmara University School of Medicine with the protocol number of 09.2011.0031. Between January 2005 and June 2010, 13 (12 male: 1 female) patients who had histologically proven, locally advanced (AJCC IB-IIIB) gastric cancer and who had undergone an operation were recruited for the analysis (Edge et al., 2010). Their median age was 61 (range, 48–74 years), and all of the patients followed were disease-free, with no clinically diagnosed kidney insufficiency. There were two patients had comorbidities (hypertension and diabetes) diagnosed before adjuvant radiotherapy.

2.1. *Chemoradiotherapy*

All patients underwent our center's routine procedure for upper abdominal region tumors. The patients first underwent a simulation in the supine position and then a treatment-planning computed tomography scan (CT) with images taken at 5-mm slice intervals. The data were transferred to a treatment planning system (Eclipse v8.0 Varian Medical Systems, Palo Alto, USA), and 3D planning was performed for all patients. Two opposite and equally weighted anterior–posterior fields were used. Treatment was administered with photons (18 MV) using a linear accelerator (Saturne 42, 800 series, General Electric, Buc, France). A total median dose of 45 Gy (range, 45–50.4 Gy) in 25–28 daily fractions of 1.8 Gy was delivered to the target (primary tumor site and regional lymphatics). Concurrent chemotherapy was administered as an IV bolus of 5-fluorourasil 400 mg/m^2/day and leucovorin 20 mg/m^2/day during the first four and last three fractions of radiotherapy (Macdonald et al., 2001). Chemotherapy was administered to 84.6% of patients without any interruption due to any toxicity. All patients had one cycle of chemotherapy before radiotherapy and one more cycle after concurrent treatment.

2.2. *Kidney anatomy and function analysis*

Kidney volumes were calculated for the CT-simulation images and last follow-up abdominal CT images using a standardized formula ($V = p/6 \times \text{height} \times \text{width} \times \text{length}$). The percentages of difference between the two images were also calculated. Creatinine clearance was calculated using the Cochroft formula of glomerular filtration rate (GFR) [(140−age) × kg/72 × creatinine] (www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). Serum creatinine was measured using the kinetic color test (Jaffé method) for the quantitative determination of creatinine in human serum on Beckman Coulter analysers. Reference intervals for serum creatinine were as follows:

Male <50 years 74–110 μmol/L (0.84–1.25 mg/dL)
Male >50 years 72–127 μmol/L (0.81–1.44 mg/dL)
Female 58–96 μmol/L (0.66–1.09 mg/dL)

Patient serum samples were used to compare this Creatinine OSR6178 assay on the AU2700 against a commercially available enzymatic creatinine assay which has demonstrated equivalence to the IDMS reference method.

Renal insufficiency grading was performed according to the recommendations of the American Kidney Society (www.kidney.org/professionals/KDOQI/guidelines_commentaries.cfm).

2.3. *Dynamic renal scintigraphy with mercaptoacetyltriglycine (MAG3)*

Each patient was asked to drink a minimum of 500 ml of water 15–30 min before the scan. After the i.v. bolus injection of 2 mCi Tc-99m MAG3 (Technescan MAG3™ Kit, Mallinckrodt Pharmaceuticals, Ireland), images were acquired every second for 60 s in the perfusion phase and every 30 s for 23 min in the extraction and excretion phases (Symbia® E Gamma Camera System, Siemens, USA) according to European Association of Nuclear Medicine dynamic renography guideline (Gordon, Piepsz, & Sixt, 2011). The images were evaluated both visually and semiquantitatively (split function, time to peak and time from maximum activity to 1/2 maximum activity) by drawing regions of interest around each kidney, both of which were assumed to contribute equally to the total renal function (the split function was 50% for both) before radiotherapy. According to these terms, a split function of the left kidney was calculated after therapy and was correlated with the other findings.

2.4. *Dose-volume analysis*

Dose volume histograms were derived from the treatment plans for each patient. The percentages receiving 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25), 30 Gy (V30), 35 Gy (V35), 40 Gy (V40), maximum dose (Dmax) and mean dose (Dmean) volumes for the total (combined) kidney and for

the main (left) kidney were calculated. The percentages change in creatinine and GFR; percentage losses in total kidney volume and left kidney volume; and the percentage of functional left kidney were also calculated.

2.5. *Statistical analysis*

Paired sample t-tests were used to compare the pre- and post-radiotherapy results of serum creatinine, GFR and kidney volumes for each patient. The percentages of difference between pre- and post-radiotherapy creatinine, GFR, and kidney volumes were evaluated. Spearman correlation analysis was performed to assess the correlations between the percentages of changes in these parameters and each of the dose-volume results (V5 to V40, Dmax, and Dmean). Multivariate analysis was performed for gender, age and comorbidity. Statistical significance was set at $p < 0.05$.

3. Results

The median follow-up was 55 months (range, 20–84 months). The morphological and functional results of kidneys were summarized in Table 1. There was no statistically significant difference in the creatinine level changes. However, the glomerular filtration rate (98.2 ± 22.8 mg/dL vs. 83.36 ± 15.8 mg/dL, $p = 0.03$), total kidney volume (355 ± 72.6 cc vs. 320.6 ± 74.9 cc, $p = 0.02$) and left kidney volume (185.7 ± 41.5 vs. 151.1 ± 46.02, $p < 0.0001$) were significantly decreased during follow-up. All patients' basal GFR results were higher than 60 ml/min. In six patients, the basal GFR results were between 60 and 90 ml/min (mean 80.7 ml/min); in seven patients, the basal GFR results were greater than 90 ml/min (mean 117.6 ml/min). The percentages of changes in the study parameters for all patients and for the low GFR group are shown in Table 2. All of the correlation results are summarized in Tables 3 and 4. According to the dose-volume results, there were correlations between V35 (20.6%) and the percentages of left kidney volume loss ($p = 0.035$) and left kidney functional loss ($p = 0.027$) and between V40 and the percentages of left kidney volume loss ($p = 0.031$) and functional loss ($p = 0.019$) (Table 3). In the low GFR group, V5 (45.2%, $p = 0.03$), V10 (35%, $p = 0.02$), V15 (30.1%, $p = 0.02$), V20 (27.2%, $p = 0.02$), V25 (24.5%, $p = 0.02$), V30 (22%, $p = 0.02$), V35 (20.6%, $p = 0.02$), V40 (15.7%, $p = 0.02$) and Vmean (29.9%) ($p = 0.008$) were correlated with the percentage of left kidney functional loss. A correlation was also noted between Vmean and left kidney volume loss ($p = 0.045$). Moreover, V10 (24.4%, $p = 0.04$), V15 (20.3%, $p = 0.01$), V20 (18.2%, $p = 0.009$), V25 (15.7%, $p = 0.009$), V30 (13.4%, $p = 0.006$), V35 (11.5%, $p = 0.007$) and V40 (9.3%, $p = 0.014$) correlated with the percentage of total kidney functional loss (Table 4). On multivariate analysis, no significant results were found for these parameters.

Table 1 – Comparison of renal function results for the pre- and post-treatment periods.

	Mean (±SD)	*p*
Creatinine (mg/dL)		
Before CRT	0.86 (±0.16)	0.28
After CRT	0.92 (±0.15)	
Creatinine clearance (GFR) (mg/dL)		
Before CRT	98.2 (±22.8)	0.03
After CRT	83.36 (±15.8)	
Total kidney volume (cc)		
Before CRT	355 (±72.6)	0.02
After CRT	320.6 (74.9)	
Main kidney volume (cc)		
Before CRT	185.7 (±41.5)	<0.0001
After CRT	151.1 (±46.02)	

4. Discussion

None of the patients suffered from clinical renal insufficiency after a median 55 months of follow-up in our study. Conversely, the left kidney volume was decreased, as correlated mostly with the higher doses of 35 Gy and 40 Gy. Due to the dose-volume analysis, the volume loss in the left kidney was also accompanied by a loss of functional impairment. Here, we also used mercaptoacetyltriglycine (MAG3) which is a tubular agent. It has a high renal extraction rate with an improved image quality (even in patients with deteriorated renal function) compared to the other agents. mercaptoacetyltriglycine is now the radiopharmaceutical of choice in dynamic renal scans, which were completed using the Tc-99m MAG3 test (Gordon et al., 2011). In contrast, there were no similar results considering the anatomical and functional losses in both kidneys, which could be explained by the compensatory functions of the kidneys. When lower doses of irradiation were received partially by one kidney, the remainder of that kidney and the opposite kidney demonstrate an increase in glomerular filtrations and compensatory functions (hyperfiltration). Therefore, as previously described, the kidney tolerance dose is determined by the number of tubule cells per nephron rather than the number of nephrons per kidney (Emami et al., 1991). Still, such effects may progress to glomerular sclerosis (Helal et al., 2012). Moreover, for partial kidney irradiation, mean dose limit for both kidneys was recommended to keep below 18 Gy (Nevinny-Stickel et al., 2007). In our study, we found that the mean dose was 9.5 Gy which was as low as recommended in literature. The other reference doses that may be used as a predictor for

Table 2 – Percentage changes in all patients and in GFR low patients.

	Mean (±SD)	
	All patients n = 13	GFR low group n = 6
Percentage of loss in whole kidney volume (%)	12.33	14.95
Percentage of loss in left kidney volume (%)	19.68 (±10.95)	20.27 (±12.43)
Percentage of loss in functional role of left kidney (%)	10.15 (±9.35)	10.11 (±10.22)
Percentage of change in creatinine (%)	13.17 (±14.09)	6.60 (±6.77)
Percentage of change in clearance (%)	15.57 (±13.07)	9.33 (±8.99)

Table 3 – Correlation results for all patients (n = 13).

	Percentage of change in creatinine (%)		Percentage of change in clearance (%)		Percentage of loss in total kidney volume (%)		Percentage of loss in left kidney volume (%)		Percentage of loss in functional role of left kidney (%)	
	p	r	p	r	p	r	p	r	p	r
Left kidney										
V5 (45.7%)	0.457	0.227	0.286	0.320	0.517	−0.19	0.122	0.451	0.129	0.444
V10 (35.01%)	0.679	0.127	0.491	0.21	0.72	−0.1	0.067	0.522	0.055	0.543
V15 (30.1%)	0.83	0.066	0.625	0.149	0.725	−0.088	0.071	0.516	0.089	0.490
V20 (27.2%)	0.95	0.019	0.7	0.116	0.872	−0.05	0.067	0.523	0.072	0.514
V25 (24.5%)	0.957	0.017	0.8	0.077	0.986	0.006	0.052	0.549	0.068	0.521
V30 (22%)	0.957	0.017	0.8	0.077	0.986	0.006	0.052	0.549	0.068	0.521
V35 (20.6%)	0.914	0.033	0.858	0.055	0.823	0.069	0.035	0.588	0.027	0.609
V40 (15.7%)	0.733	0.10	1.0	0	0.68	0.127	0.031	0.599	0.019	0.636
Vmax (46.2%)	0.524	0.19	0.86	0.053	0.50	0.20	0.171	0.404	0.016	0.649
Vmean (9.5%)	0.99	0.003	0.77	0.089	0.943	−0.02	0.056	0.542	0.054	0.545
Total kidney										
V5 (32.9%)	0.351	0.282	0.136	0.436	0.487	0.21	0.344	0.286	0.577	0.171
V10 (24.4%)	0.893	0.041	0.439	0.235	0.347	−0.28	0.329	0.294	0.239	0.352
V15 (20.3%)	0.986	−0.006	0.5	0.2	0.4	−0.25	0.28	0.324	0.23	0.358
V20 (18.2%)	0.943	0.022	0.457	0.227	0.481	−0.21	0.20	0.374	0.197	0.383
V25 (15.7%)	0.143	0.022	0.457	0.227	0.481	−0.21	0.209	0.374	0.197	0.383
V30 (13.4%)	0.986	0.006	0.502	0.205	0.475	−0.21	0.177	0.399	0.18	0.394
V35 (11.5%)	0.943	0.022	0.5	0.2	0.426	−0.24	0.174	0.4	0.18	0.397
V40 (9.3%)	0.7	−0.11	0.76	0.094	0.865	−0.05	0.06	0.534	0.132	0.441
Vmax (46.5%)	0.015	−0.65	0.064	−0.52	0.979	0.008	0.1	0.475	0.114	0.46
Vmean (29.9%)	0.857	−0.056	0.638	0.144	0.351	−0.18	0.221	0.365	0.406	0.252

radiation-induced renal injury in literature was summerized in Table 5. Therefore, it seems that all findings of our study was lower than the results of previous studies (Jansen et al., 2007; Nevinny-Stickel et al., 2007 and Welz et al., 2007). Our study showed that, despite of the low doses, there may be found impairment of functional capacity in kidneys. One of the most important sign of renal insufficiency is the decreases of creatinine clearance. In one study, authors showed that the creatinine clearance decreases if half of one kidney's dose exceeds 26 Gy (Willett et al., 1986). Another study reported

Table 4 – Correlation results in low basal GFR patients (n = 6).

	Percentage of change in creatinine (%)		Percentage of change in clearance (%)		Percentage of loss in total kidney volume (%)		Percentage of loss in left kidney volume (%)		Percentage of loss in functional role of left kidney (%)	
	p	r	p	r	p	r	p	r	p	r
Left kidney										
V5 (45.7%)	0.398	0.322	0.235	0.441	0.865	0.067	0.099	0.583	0.034	0.706
V10 (35.01%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
V15 (30.1%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
V20 (27.2%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
V25 (24.5%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
V30 (22%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
V35 (20.6%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
V40 (15.7%)	0.509	0.254	0.277	0.407	0.831	0.083	0.077	0.617	0.02	0.748
Vmax (46.2%)	0.592	−0.2	0.982	−0.009	0.81	−0.09	0.345	0.358	0.133	0.541
Vmean (9.5%)	0.625	0.19	0.338	0.362	0.728	0.136	0.045	0.678	0.008	0.812
Total kidney										
V5 (32.9%)	0.965	0.017	0.60	0.203	0.831	0.083	0.18	0.483	0.12	0.546
V10 (24.4%)	0.828	0.085	0.398	0.322	0.865	−0.067	0.38	0.333	0.04	0.681
V15 (20.3%)	0.897	0.051	0.425	0.305	0.831	−0.083	0.35	0.350	0.01	0.765
V20 (18.2%)	0.761	0.119	0.323	0.373	0.966	−0.017	0.22	0.450	0.009	0.807
V25 (15.7%)	0.761	0.119	0.323	0.373	0.966	−0.017	0.22	0.450	0.009	0.807
V30 (13.4%)	0.845	0.077	0.4	0.315	0.949	−0.02	0.168	0.502	0.006	0.827
V35 (11.5%)	0.761	0.119	0.425	0.3	0.831	−0.08	0.170	0.5	0.007	0.815
V40 (9.3%)	0.948	−0.02	0.612	0.197	0.932	0.034	0.15	0.52	0.014	0.775
Vmax (46.5%)	0.5	−0.25	0.895	−0.052	0.631	−0.18	0.347	0.356	0.073	0.624
Vmean (9.5%)	0.86	−0.69	0.723	0.138	0.828	0.085	0.235	0.441	0.127	0.547

Table 5 – Comparisons of the dose limits for radiation-induced kidney injury in different studies.

Variable	Dose-volume relations	Reference	Our study
Partial kidney irradiation			
Bilateral kidneys	Mean kidney dose <18 Gy	Nevinny-Stickel et al., 2007	9.5 Gy
Bilateral kidneys	V28Gy < %20	Nevinny-Stickel et al., 2007	14.5%
Bilateral kidneys	V20Gy < %32	Jansen et al., 2007	18.2%
Bilateral kidneys	V12Gy < %55	Welz et al., 2007	22.5%

that creatinine clearance decreases if the total renal dose exceeds 10–20 Gy in 0.8–1.25 Gy per fraction (Schneider, Marti, Von Briel, Frey, & Greiner, 1999). In our study, we observed a decline in creatinine clearance for all patients. It was more prominent in patients that the pre-treatment GFR results were 60–90 ml/min.

Based on these data, conformal treatment recommends that V35 be kept under 20.5%, and V40, below 15.7%, in order to reduce the anatomical and functional kidney damage within the treatment field. V28 for bilateral renal irradiation is recommended to be kept under 20%; our study used the value of 14.5%. Several reasons could have accounted for our inability to demonstrate significant dose-volume proposals for the bilateral kidneys, among which are the low number of patients and the compensatory features of the kidney.

During treatments that place the kidneys within the radiotherapy field, it is not routine to modify the dosage in patients due to a mild to moderate decrease in the GFR. In our subgroup analysis, patients with mildly or moderately low baseline GFR values had prominent functional impairment in the left kidney at low doses. The present analysis of all patients showed no significant effect on the bilateral kidneys, although the designation of kidney damage in this group included not only the left kidney but also both kidneys. According to these guidelines, our study showed that even in the range of a so-called “safe dose” a significant effect may occur on kidneys of patients with functional basal causes. Therefore, based on our results, the baseline renal function of patients should be examined in detail before radiotherapy.

In conclusion, functional injury may help to predict the clinical insufficiency for kidneys after chemoradiotherapy. This effect is more prominent in patients who have mildly or moderately low GFR. Hence, basal renal functions should be assessed, and comorbid factors should be considered before radiotherapy. Renal toxicity seems to act as an iceberg; not only for high doses but also for low doses and more attention may be recommended during treatment planning.

Conflict of interest

We declare that we have no conflict of interest.

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